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Published in:
Journal of the American Heart Association

DOI:
[10.1161/JAHA.119.014160](https://doi.org/10.1161/JAHA.119.014160)

Publication date:
2020

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Ravn Jacobsen, M., Jabbari, R., Glinge, C., Kjær Stampe, N., Butt, J. H., Blanche, P., Lønborg, J., Wendelboe Nielsen, O., Køber, L., Torp-Pedersen, C., Pedersen, F., Tfelt-Hansen, J., & Engstrøm, T. (2020). Potassium Disturbances and Risk of Ventricular Fibrillation Among Patients With ST-Segment-Elevation Myocardial Infarction. *Journal of the American Heart Association*, 9(4), [e014160]. <https://doi.org/10.1161/JAHA.119.014160>

Potassium Disturbances and Risk of Ventricular Fibrillation Among Patients With ST-Segment–Elevation Myocardial Infarction

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Background—Potassium disturbances per se increase the risk of ventricular fibrillation (VF). Whether potassium disturbances in the acute phase of ST-segment–elevation myocardial infarction (STEMI) are associated with VF before primary percutaneous coronary intervention (PPCI) is uncertain.

Methods and Results—All consecutive STEMI patients were identified in the Eastern Danish Heart Registry from 1999 to 2016. Comorbidities and medication use were assessed from Danish nationwide registries. Potassium levels were collected immediately before PPCI start. Multivariate logistic models were performed to determine the association between potassium and VF. The main analysis included 8624 STEMI patients of whom 822 (9.5%) had VF before PPCI. Compared with 6693 (77.6%) patients with normokalemia (3.5–5.0 mmol/L), 1797 (20.8%) patients with hypokalemia (<3.5 mmol/L) were often women with fewer comorbidities, whereas 134 (1.6%) patients with hyperkalemia (>5.0 mmol/L) were older with more comorbidities. After adjustment, patients with hypokalemia and hyperkalemia had a higher risk of VF before PPCI (odds ratio 1.90, 95% CI 1.57–2.30, $P<0.001$) and (odds ratio 3.36, 95% CI 1.95–5.77, $P<0.001$) compared with normokalemia, respectively. Since the association may reflect a post-resuscitation phenomenon, a sensitivity analysis was performed including 7929 STEMI patients without VF before PPCI of whom 127 (1.6%) had VF during PPCI. Compared with normokalemia, patients with hypokalemia had a significant association with VF during PPCI (odds ratio 1.68, 95% CI 1.01–2.77, $P=0.045$) after adjustment.

Conclusions—Hypokalemia and hyperkalemia are associated with increased risk of VF before PPCI during STEMI. For hypokalemia, the association may be independent of the measurement of potassium before or after VF. (*J Am Heart Assoc.* 2020;9:e014160. DOI: 10.1161/JAHA.119.014160.)

Key Words: potassium disturbances • ST-segment–elevation myocardial infarction • ventricular fibrillation

Coronary artery disease leading to myocardial infarction (MI) is the leading cause of sudden cardiac death.^{1–4} Ventricular fibrillation (VF) complicating ST-segment–elevation myocardial infarction (STEMI) occurs in \approx 10% of patients^{5,6} and remains a challenge for physicians as VF may be the first symptom of underlying cardiovascular disease.

Potassium disturbances are one of the most common electrolyte abnormalities.⁷ The role of potassium disturbances

in the setting of MI has been studied, with a higher frequency of ventricular arrhythmias observed for low potassium levels (typically <3.5 mmol/L).^{8–10} Although these findings highlight the importance of potassium disturbances as a risk factor for VF among MI patients,¹¹ many of these studies were conducted in a time before the era of PPCI,^{8–10} included a relatively small number of patients,^{8,10} and defined the outcome as cardiac arrest; therefore, a proportion of the arrests may not have been

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Accompanying Table S1 through S6 and Figures S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014160>

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Received August 15, 2019; accepted December 3, 2019.

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Clinical Perspective

What Is New?

- ST-segment–elevation myocardial infarction (STEMI) patients with hypo- and hyperkalemia had a higher risk of ventricular fibrillation (VF) before primary percutaneous coronary intervention (PPCI) compared with normokalemia, but the association may reflect a post-resuscitation phenomenon as potassium was measured immediately before PPCI, hence after VF.
- For STEMI patients with in-hospital VF before PPCI with a short time window between potassium measurement and VF, hypokalemia remained associated with VF compared with normokalemia.
- Among STEMI patients without VF before PPCI who had potassium measurements immediately before PPCI, hypokalemia was associated with VF during PPCI.

What Are the Clinical Implications?

- Potassium disturbances among STEMI patients may increase the risk of VF before PPCI and subsequent death during acute ischemia.
- Further studies are needed to determine if correcting potassium disturbances will reduce the risk of VF before PPCI among patients with STEMI.

VF.¹² Furthermore, none of these studies distinguished between STEMI and non-STEMI patients. Both conditions arise from the same pathogenesis,¹³ but may not be comparable in risk assessment for VF as the burden of VF is lower among non-STEMI patients (2%).^{14,15}

Recently, in a large cohort of MI patients, a U-shaped relationship between post-admission potassium levels and in-hospital mortality was observed and increased rates of cardiac arrest during hospitalization demonstrated for the lowest (<3.0 mmol/L) and highest (≥5.0 mmol/L) potassium levels.¹² However, this study was underpowered in regard to the number of VF, possibly because of misclassification of the cardiac arrest diagnosis. While recent studies have demonstrated prognostic effects of potassium disturbances in the inpatient setting,^{12,16} no study has investigated the risk of potassium disturbances for developing VF in the early, and potentially modifiable, ischemic phase of an acute MI (before PPCI).

The aim of this study was to determine the association between potassium disturbances and the risk of VF before PPCI among STEMI patients. Since potassium disturbances may reflect a post-resuscitation phenomenon, a sensitivity analysis was performed including STEMI patients with VF during PPCI who had potassium measurements before PPCI and, thereby, before VF.

Methods

Anonymized data created for the study are available in a persistent repository.

Study Design and Data Sources

This single-center cohort study included patients aged ≥18 years with STEMI (Figure 1). Clinical data from the Eastern Danish Heart Registry were used. This registry comprises detailed clinical, angiographic, and procedural characteristics on all consecutive STEMI patients who underwent cardiac catheterization and coronary revascularization at Copenhagen University Hospital, Rigshospitalet since October 21, 1999. These data have been registered routinely by all operators and assistants in the catheterization laboratory during percutaneous coronary intervention. Until June 1, 2011 Rigshospitalet had a catchment area for PPCI of 1.7 million inhabitants (30% of the entire Danish population), and from then on Rigshospitalet has covered all eastern Denmark corresponding to 2.5 million (45% of the entire Danish population).⁵

Data were linked to Danish nationwide administrative registries via the Civil Registration Number. All residents in Denmark receive a unique, personal, and permanent Civil Registration Number, which enables individual linkage of nationwide healthcare-related registries unambiguously. Information on vital status and the date of birth was retrieved from the Danish Civil Registration System.¹⁷ The Danish National Patient Register holds information on all hospital admissions and outpatient contacts according to the *International Classification of Disease, Eighth and Tenth Revisions (ICD-8 and ICD-10)*,¹⁸ and the date of admission, discharge, and diagnoses was retrieved for every patient before the STEMI index admission (Table S1). Information on dispensed medicine 3 months before the STEMI index was collected from the Danish National Prescription Registry, which holds information on all dispensed medical prescriptions from Danish pharmacies based on the Anatomical Therapeutic Chemical System codes including type of drug, dispensing date, strength, and quantity of all claimed drug prescriptions (Table S2).¹⁹ Hypertension, diabetes mellitus, and hypercholesterolemia were identified according to diagnosis either from hospital admissions or outpatient contacts and in addition from dispensed medication (antihypertensives, antidiabetics, and cholesterol-lowering drugs, respectively) 3 months before STEMI index.

Data on blood levels were obtained from an electronic laboratory database with several blood samples and their exact time of measurement. Blood samples immediately before PPCI were selected. Potassium levels were categorized in 3 preselected intervals: hypokalemia <3.5 mmol/L, normokalemia 3.5–5.0 mmol/L, and hyperkalemia >5.0 mmol/L.

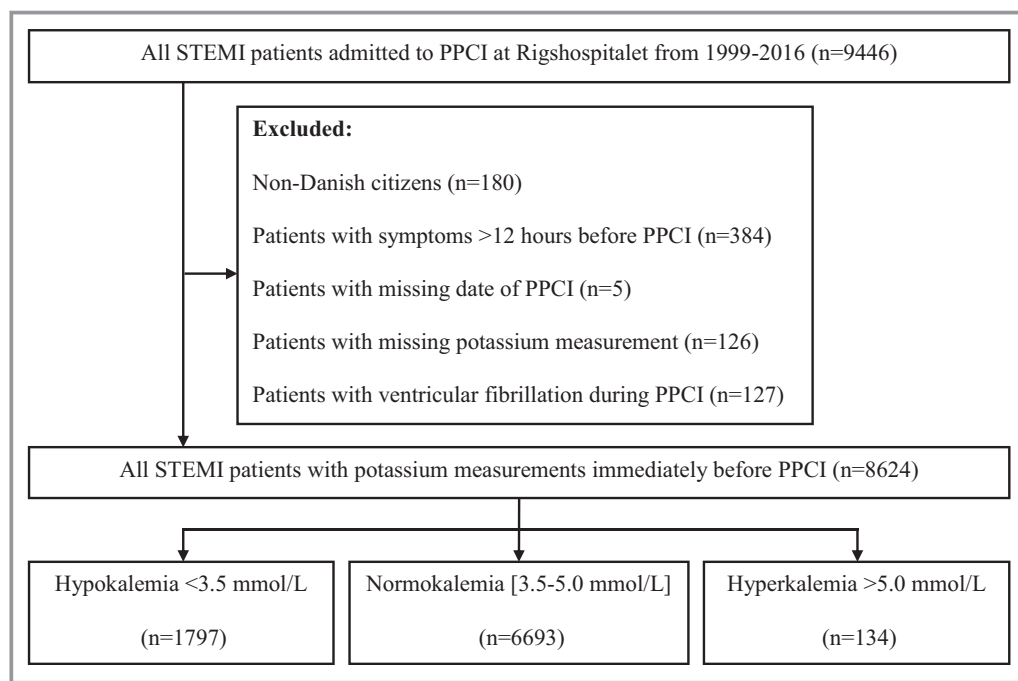


Figure 1. Flowchart illustrating the selection of patients with STEMI admitted to primary percutaneous coronary intervention at Rigshospitalet from 1999 to 2016. PPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction.

Study Population

To qualify for the study, patients had to have symptoms lasting ≤ 12 hours and acute ST-segment elevation on an ECG. All patients underwent angiography and subsequent PPCI, and only the first admission to PPCI in patients with multiple admissions was considered.

The primary outcome was VF or sustained pulseless ventricular tachycardia (VT) (≥ 30 seconds and/or clinical cardiac arrest) within 12 hours of symptoms and before catheter insertion for PPCI. All medical reports and discharge summaries were reviewed to verify the VF diagnosis. Both out-of-hospital and in-hospital cardiac arrest (but before PPCI) patients were included. Patients with out-of-hospital cardiac arrest were included upon admission to the PCI-center after resuscitation by emergency medical service personnel. Patients with VF during PPCI were excluded from the main analysis as the arrhythmogenesis may be different and related to catheter maneuvers.

Since potassium levels were measured after VF but before PPCI, a sensitivity analysis was conducted to examine the association between potassium levels before VF and the risk of developing VF. STEMI patients with VF before PPCI were excluded and patients with VF during PPCI were identified, and they had potassium measurements immediately before PPCI and, thereby, before VF.

Statistical Analysis

The baseline and angiographic characteristics are presented as the median and interquartile range or proportion for the potassium groups. Statistical significance related to the descriptive differences were computed using the Wilcoxon rank-sum test for continuous variables and the Chi-square test (or Fisher exact test when appropriate) for categorical variables. A 2-tailed $P \leq 0.05$ was considered statistically significant.

Logistic regression models were constructed to examine whether potassium disturbances were independent risk factors for VF among STEMI patients. Adjusted odds ratios (OR) and accompanying 95% confidence intervals (CI) were computed to estimate the associations. Multivariate logistic models were performed by including any covariate preceding the STEMI that is known to increase the risk of VF: age, sex, previous history of chest pain, smoking, hypertension, prior myocardial infarction, congestive heart failure, atrial fibrillation, acute creatinine levels, Killip class at admission, culprit lesion, and preprocedural thrombolysis in myocardial infarction (TIMI) flow.^{5,6,20–22} Peripheral vascular disease and diabetes mellitus were included in the model, as these comorbidities were independently associated with VF in this cohort. Smoking and Canadian Cardiovascular Society grading of angina pectoris were later removed from the model because of a large amount of missing information of 12% and

Table 1. Characteristics of Patients With STEMI Who Had Potassium Measurements Immediately Before Primary Percutaneous Coronary Intervention

Variables	Normokalemia 3.5 to 5.0 mmol/L (n=6693)	Hypokalemia <3.5 mmol/L (n=1797)	P Value Hypokalemia Vs Normokalemia	Hyperkalemia >5.0 mmol/L (n=134)	P Value Hyperkalemia Vs Normokalemia
Male sex, n (%)	5145 (76.9)	1178 (65.6)	<0.001	99 (73.9)	0.50
Median age, y [IQR]	63.0 [53.9, 71.9]	62.7 [53.5, 72.0]	0.57	68.5 [60.2, 76.9]	<0.001
Categorical age, n (%)					
<50 y	1070 (16.0)	302 (16.8)	0.62	11 (8.2)	0.003
50 to 80 y	4908 (73.3)	1312 (73.0)		99 (73.9)	
≥80 y	715 (10.7)	183 (10.2)		24 (17.9)	
Body mass index (BMI), kg/m ²					
BMI ≥25, n (%)	3270 (62.3)	897 (64.5)	0.14	59 (63.4)	0.90
Smoking, n (%)					
Current	3069 (52.3)	762 (48.4)	<0.001	45 (47.4)	0.62
Past	1480 (25.2)	382 (24.3)		27 (28.4)	
Never	1318 (22.5)	430 (27.3)		23 (24.2)	
Canadian cardiovascular society grading of angina pectoris, n (%)					
Class I to II	735 (12.1)	182 (11.1)	0.25	15 (14.7)	0.50
Class III to IV	587 (9.7)	144 (8.8)		7 (6.9)	
No angina	4753 (78.2)	1316 (80.1)		80 (78.4)	
Comorbidities, n (%)					
Diabetes mellitus	789 (11.8)	157 (8.7)	<0.001	41 (30.6)	<0.001
Hypertension	1692 (25.3)	667 (37.1)	<0.001	62 (46.3)	<0.001
Hypercholesterolemia	1220 (18.2)	310 (17.3)	0.36	35 (26.1)	0.026
Peripheral vascular disease	284 (4.2)	45 (2.5)	<0.001	14 (10.4)	0.001
Family history of ischemic heart disease	1719 (32.5)	466 (33.5)	0.51	18 (28.6)	0.60
Ischemic heart disease	1356 (20.3)	335 (18.6)	0.14	39 (29.1)	0.016
Prior myocardial infarction	827 (12.4)	177 (9.8)	0.004	30 (22.4)	<0.001
Congestive heart failure	312 (4.7)	64 (3.6)	0.05	14 (10.4)	0.004
Atrial fibrillation	290 (4.3)	71 (4.0)	0.52	20 (14.9)	<0.001
Stroke	310 (4.6)	72 (4.0)	0.28	9 (6.7)	0.35
Chronic kidney disease	194 (2.9)	39 (2.2)	0.11	17 (12.7)	<0.001
Liver disease	87 (1.3)	29 (1.6)	0.37	≤3 (≤2.2)	1.00
Outcome, n (%)					
Ventricular fibrillation before PPCI	548 (8.2)	242 (13.5)	<0.001	32 (23.9)	<0.001
Pharmacotherapy, n (%)					
Diuretics (combinational)	265 (4.0)	187 (10.4)	<0.001	5 (3.7)	1.00
Loop diuretics	292 (4.4)	82 (4.6)	0.76	19 (14.2)	<0.001
Thiazides	357 (5.3)	256 (14.2)	<0.001	8 (6.0)	0.90
Spironolactone	64 (1.0)	13 (0.7)	0.43	9 (6.7)	<0.001
Potassium supplements	210 (3.1)	98 (5.5)	<0.001	13 (9.7)	<0.001
Renin-angiotensin-system blockers	1198 (17.9)	386 (21.5)	<0.001	37 (27.6)	0.005

Continued

Table 1. Continued

Variables	Normokalemia 3.5 to 5.0 mmol/L (n=6693)	Hypokalemia <3.5 mmol/L (n=1797)	P Value Hypokalemia Vs Normokalemia	Hyperkalemia >5.0 mmol/L (n=134)	P Value Hyperkalemia Vs Normokalemia
Beta-blockers	827 (12.4)	208 (11.6)	0.39	25 (18.7)	0.040
Anti-adrenergic drugs	57 (0.9)	16 (0.9)	0.99	0 (0.0)	0.55
Calcium channel blockers	728 (10.9)	335 (18.6)	<0.001	20 (14.9)	0.18
Antidiabetics	602 (9.0)	113 (6.3)	<0.001	33 (24.6)	<0.001
Statins	940 (14.0)	224 (12.5)	0.09	25 (18.7)	0.16
Antiarrhythmic drugs class I and III	8 (0.1)	≤3 (≤1.7)	0.74	≤3 (≤2.2)	0.003
Blood samples					
Acute creatinine, $\mu\text{mol/L}$ [IQR]	78.0 [66.0, 94.0]	76.0 [64.0, 91.0]	<0.001	126.5 [97.0, 168.5]	<0.001
Troponin-T max, ng/L [IQR]	3775 [1500, 7490]	3560 [1360, 7520]	0.10	5110 [1700, 13 300]	0.007
Time from symptom to troponin-T max, h [IQR]	13.8 [9.6, 18.0]	13.9 [9.8, 18.7]	0.15	15.5 [9.1, 21.3]	0.23

Missing: BMI 22%, smoking 13%, family history of ischemic heart disease 22%, Canadian Cardiovascular Society class 9%, acute creatinine 7%, troponin-T max 20%, and time from symptoms to troponin-T max 20%. BMI indicates body mass index; IQR, interquartile range. STEMI indicates ST-segment-elevation myocardial infarction.

9%, respectively. Use of diuretic medication (loop diuretics, combinational diuretics, thiazides, and spironolactone) 3 months before STEMI index was also included. Prior use of antiarrhythmic therapy (class I and III agents) may reduce the risk of VF in the setting of STEMI. However, since <0.2% of patients were treated with antiarrhythmic drugs 3 months before STEMI index, treatment with antiarrhythmic drugs was not included in the model. Finally, maximum troponin-T levels measured during hospitalization (within 3 days after STEMI index) was included.

Additional analysis adjusted for age, sex, and acute creatinine levels was conducted to illustrate the relationship between potassium and VF before PPCI. The same potassium measurements and comparison groups were used but the hypokalemia group was divided into severe (2.1–2.7 mmol/L) and mild hypokalemia (2.8–3.4 mmol/L). The hyperkalemia group had too few patients to perform further substratification.

Furthermore, a subpopulation of STEMI patients with in-hospital VF before PPCI was studied (excluding STEMI patients with out-of-hospital VF). In this way, the time window between VF and potassium measurement would be short and the VF anticipated to be treated immediately. A logistic regression model was performed to evaluate the association between potassium disturbances and risk of in-hospital VF before PPCI adjusted for age, sex, and acute creatinine levels.

Finally, a logistic regression model was conducted in the sensitivity analysis to emphasize the association between potassium disturbances and VF during PPCI adjusted for age, sex, cardiovascular comorbidities (hypertension, prior myocardial infarction, congestive heart failure, atrial fibrillation, diabetes mellitus, and peripheral vascular disease), acute creatinine levels, maximum troponin-T levels, Killip class,

culprit lesion, preprocedural TIMI flow, and use of diuretic medication.

Analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and RStudio (version 3.4).

Ethics Approval

The study was approved by the Danish Data Protection Agency (2007-58-0015/GEH-2014-014 and I-suite number: 02732). Registers were available in an anonymous setup; individual patients were not identifiable because the Civil Registration Numbers were encrypted. Approval from the Danish Patient Safety Authority was received to gain information on medical reports and discharge summaries (No. 3-3013-2277/1). In Denmark ethical approval is not required for retrospective register-based studies.

Results

Out of 9446 consecutively enrolled STEMI patients, 8624 (91%) STEMI patients with potassium measurements immediately before PPCI were included, of whom 1797 (20.8%) had hypokalemia (<3.5 mmol/L), 6693 (77.6%) had normokalemia [3.5–5.0 mmol/L], and 134 (1.6%) had hyperkalemia (>5.0 mmol/L). The distribution of potassium approached that of a normal distribution with a mean of 3.8 mmol/L (SD: 0.5) (Figure S1).

Clinical Characteristics

Among the 8624 included STEMI patients, 822 (9.5%) had VF before PPCI. Of the 822 STEMI with VF, 49 (6%) developed sustained pulseless VT. The majority had out-of-hospital

Table 2. Angiographic and Procedural Characteristics of Patients With STEMI Who Had Potassium Measurements Immediately Before Primary Percutaneous Coronary Intervention

Variables	Normokalemia 3.5 to 5.0 mmol/L (n=6693)	Hypokalemia <3.5 mmol/L (n=1797)	P Value Hypokalemia Vs Normokalemia	Hyperkalemia >5.0 mmol/L (n=134)	P Value Hyperkalemia Vs Normokalemia
Time from symptom onset to PPCI, min [IQR]	188 [132–280]	145 [108–230]	<0.001	198 [138–330]	0.21
Preprocedural LVEF, n (%)					
≤35%	346 (26.1)	107 (28.2)	0.44	27 (64.3)	<0.001
Infarct location, n (%)					
Anterior	2773 (44.6)	808 (48.6)	0.004	45 (42.1)	0.67
Non-anterior	3445 (55.4)	856 (51.4)		62 (57.9)	
Culprit lesion, n (%)					
LAD	2937 (44.1)	864 (48.4)	0.006	62 (46.6)	0.84
RCA	2748 (41.3)	683 (38.2)		53 (39.8)	
LCX	970 (14.6)	239 (13.4)		18 (13.5)	
Killip class, n (%)					
I	5841 (91.9)	1572 (91.1)	0.17	79 (64.8)	<0.001
II	284 (4.5)	94 (5.4)		10 (8.2)	
III	87 (1.4)	28 (1.6)		5 (4.1)	
IV	146 (2.3)	31 (1.8)		28 (23.0)	
Preprocedural TIMI flow, n (%)					
TIMI 0 to I	4245 (64.0)	1209 (68.3)	<0.001	104 (78.8)	<0.001
TIMI II to III	2392 (36.0)	562 (31.7)		28 (21.2)	
Postprocedural TIMI flow, n (%)					
TIMI 0 to I	163 (2.5)	45 (2.5)	0.92	11 (8.3)	<0.001
TIMI II to III	6462 (97.5)	1727 (97.5)		121 (91.7)	

Missing: Time from symptom to procedure 15%, LVEF 80%, and Infarct location 7%. IQR indicates interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

cardiac arrest (77%) and 21% had in-hospital cardiac arrest (2% with missing information).

Baseline and angiographic characteristics are summarized in Tables 1 and 2. Compared with normokalemia, patients with hypokalemia were often women, smoked less, had fewer cardiovascular comorbidities, and lower acute creatinine levels. More often they had hypertension, used cardioactive drugs, had left anterior descending artery as culprit, and a preprocedural TIMI flow 0 to I.

Patients with hyperkalemia were older, had more cardiovascular comorbidities, used more cardioactive and antidiabetic drugs, were in Killip class >I, had pre- and post-procedural TIMI flow 0 to I, and increased levels of acute creatinine and troponin-T max compared with patients with normokalemia.

Multivariate Analysis

Younger age, male sex, atrial fibrillation, Killip class >I, left anterior descending artery as culprit, and preprocedural

TIMI flow 0 to I were all independent risk factors for VF, whereas prior myocardial infarction and diabetes mellitus were independently associated with reduced risk of VF (Table 3). Hypokalemia (OR 1.90, 95% CI 1.57–2.30, $P<0.001$) and hyperkalemia (OR 3.36, 95% CI 1.95–5.77, $P<0.001$) were associated with VF compared with normokalemia after adjusting for age, sex, cardiovascular comorbidities (hypertension, prior myocardial infarction, congestive heart failure, atrial fibrillation, diabetes mellitus, and peripheral vascular disease), acute creatinine levels, maximum troponin-T levels, Killip class, culprit lesion, preprocedural TIMI flow, and use of diuretic medication (loop diuretics, combinational diuretics, thiazides, and spironolactone) (Figure 2).

A U-shaped relationship between potassium levels and VF before PPCI was found with the highest risk for VF among patients with severe hypokalemia [2.1–2.7 mmol/L] compared with normokalemia after adjusting for age, sex, and acute creatinine levels (Figure 3).

Table 3. A Logistic Regression Model of the Risk of VF Before PPCI in STEMI Patients

Variables	Contrast	Odds Ratio	95% CI	P Value
Blood samples				
Hyperkalemia	Normokalemia	3.36	1.95 to 5.77	<0.001
Hypokalemia	Normokalemia	1.90	1.57 to 2.30	<0.001
Creatinine	10 μ mol/L of increase	1.00	1.00 to 1.01	<0.001
Troponin-T max	1000 ng/L of increase	1.01	1.00 to 1.02	0.24
Age				
<50 y of age	\geq 80 y of age	4.17	2.62 to 6.63	<0.001
50 to 80 y of age	\geq 80 y of age	3.94	2.59 to 5.99	<0.001
Sex	Men vs women	1.29	1.04 to 1.60	0.020
Hypertension	Yes vs no	1.14	0.89 to 1.45	0.29
Prior myocardial infarction	Yes vs no	0.73	0.53 to 1.00	0.048
Congestive heart failure	Yes vs no	0.60	0.35 to 1.02	0.06
Atrial fibrillation	Yes vs no	1.62	1.08 to 2.42	0.019
Diabetes mellitus	Yes vs no	0.55	0.40 to 0.75	<0.001
Peripheral vascular disease	Yes vs no	1.72	1.14 to 2.59	0.009
Killip class >I at admission	Killip class I	2.95	2.30 to 3.77	<0.001
Culprit	LAD vs non-LAD	1.58	1.32 to 1.87	<0.001
Preprocedural TIMI flow	TIMI 0 to I vs II to III	1.33	1.10 to 1.62	0.004
Loop diuretics	Yes vs no	1.10	0.68 to 1.78	0.70
Combinational diuretics	Yes vs no	0.82	0.54 to 1.23	0.33
Thiazides	Yes vs no	1.05	0.74 to 1.49	0.80
Spironolactone	Yes vs no	1.56	0.65 to 3.71	0.32

LAD indicates left anterior descending artery; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation.

Finally, a subpopulation of patients with in-hospital VF before PPCI was studied. Among the 7977 included STEMI patients without out-of-hospital VF, 175 (2.2%) had in-hospital VF before PPCI. Hypokalemia ($n=1616$) (OR 2.23, 95% CI 1.60–3.11, $P<0.001$) was associated with VF compared with normokalemia after adjusting for age, sex, and acute creatinine level (Table S3). For hyperkalemia ($n=104$) (OR 0.79, 95% CI 0.17–3.61, $P=0.76$), no significant association was found (Table S3).

Sensitivity Analysis

The sensitivity analysis included 7929 STEMI patients without VF before PPCI of whom 127 (1.6%) had VF during PPCI. Baseline and angiographic characteristics are shown in supplementary Tables S4 and S5. Patients with hypokalemia were often women, smoked less, had fewer cardiovascular comorbidities (except for hypertension), used more antihypertensive drugs, and had lower acute creatinine levels, whereas patients with hyperkalemia were older, had more cardiovascular comorbidities, and used more medications

compared with normokalemia. Compared with normokalemia, patients with hypokalemia had an OR of 1.68 (95% CI 1.01–2.77, $P=0.045$) and patients with hyperkalemia had an OR of 3.23 (95% CI 0.99–10.50, $P=0.05$) for VF after adjustment (Figure 4, and Table S6).

Discussion

In this study with consecutive data collected from 1999 to 2016, 8624 STEMI patients were enrolled, of whom 822 (9.5%) developed VF before PPCI. Increased risk of VF before PPCI was demonstrated for patients with hypokalemia [<3.5 mmol/L] and hyperkalemia [>5.0 mmol/L], and a U-shaped relationship between potassium levels and VF before PPCI was found, with the highest risk of VF among patients with severe hypokalemia [2.1–2.7 mmol/L].

Whereas patients with VF before PPCI had potassium measurements after VF that may be disturbed by the VF itself, patients with VF during PPCI had potassium measurements before VF. Importantly, hypokalemia was associated with

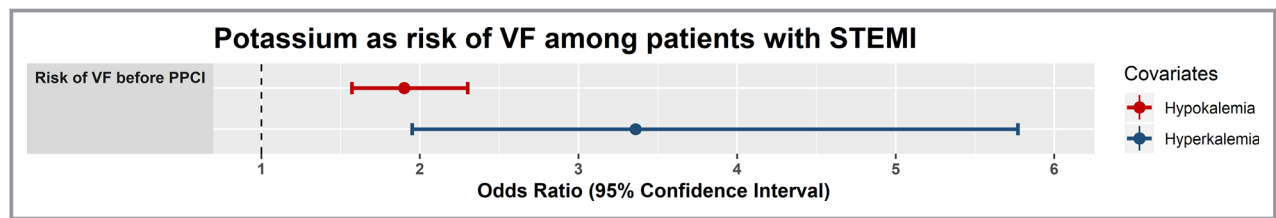


Figure 2. Potassium disturbances associated with ventricular fibrillation before primary percutaneous coronary intervention among patients with STEMI who had potassium measurements immediately before primary percutaneous coronary intervention. PPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; VF, ventricular fibrillation.

increased risk of VF during PPCI. Hence, the association between hypokalemia and VF may be independent of the measurement of potassium before or after VF.

To the best of our knowledge, this is the first comprehensive study to investigate the association between potassium disturbances and the risk of VF before PPCI. In addition to an increased risk for VF in patients with severe hypo- and hyperkalemia, our data suggested that patients with mild

hypokalemia also had a higher risk for VF. Mild hypokalemia [2.8–3.4 mmol/L] is not always considered harmful in daily clinical practice and may not be a target for immediate intervention. These findings suggest that maintenance of potassium levels between 3.5–5.0 mmol/L is advisable as currently recommended by practice guidelines in patients with AMI based on non-randomized trials.²³

Recently, Goyal and colleagues¹² investigated the correlation between mean post-admission potassium levels and mortality rates among MI patients. They found a U-shaped relationship between in-hospital mortality and potassium levels with the lowest risk between 3.5 and <4.5 mmol/L. Compared with mortality risk, they observed a relatively more flattened association between potassium levels and the risk of cardiac arrest during hospitalization. They found a significant increase in the risk of cardiac arrest for patients with hypokalemia <3.0 mmol/L after adjustment for age, sex, and glomerular filtration rate at admission. However, the number of events (cardiac arrest because of any cause) in the hypokalemia group was low (n=5), perhaps because of misclassification of the cardiac arrest diagnosis.

In this study, patients with hypokalemia had a lower burden of cardiovascular comorbidities, whereas hypertension and use of cardioactive drugs were more frequent compared with normokalemia, eg, thiazides which can cause pronounced hypokalemia during MI.²⁴ Importantly, after adjusting for use of any diuretics, the risk estimates for both hypo- and hyperkalemia remained unchanged.

Both endogenous epinephrine attributable to the cardiac arrest and exogenous epinephrine administered during resuscitation can transiently cause hypokalemia and decrease potassium by as much as 1 mmol/L.²⁵ Since potassium was measured after VF in the main analysis, hypokalemia may reflect a post-resuscitation phenomenon. However, in the sensitivity analysis, increased risk of VF was demonstrated for patients with hypokalemia measured before VF. Thus, the association between hypokalemia and VF may be independent of the measurement of potassium before or after VF. Moreover, additional analysis was performed including 175

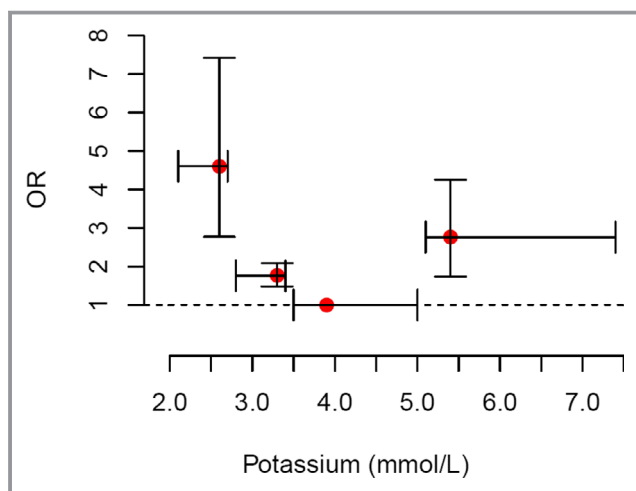


Figure 3. Association between potassium levels and risk of ventricular fibrillation before primary percutaneous coronary intervention among patients with STEMI. The x axis shows potassium measurements (mmol/L) immediately before primary percutaneous coronary intervention. The y axis shows the odds ratio of ventricular fibrillation before primary percutaneous coronary intervention adjusted for age, sex, and acute creatinine level. Each point indicates the odds ratio corresponding to the median of potassium for 4 potassium intervals: severe hypokalemia [2.1–2.7 (mmol/L); 4.61, 95% CI 2.77–7.42], mild hypokalemia [2.8–3.4 (mmol/L); odds ratio=1.76, 95% CI 1.48–2.09], normokalemia [3.5–5.0 (mmol/L); reference], hyperkalemia [5.1–7.4 (mmol/L); odds ratio 2.76, 95% CI 1.74–4.26]. The horizontal bars indicate the range of the potassium levels. The vertical bars indicate the 95% CI of the odds ratios. PPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; VF, ventricular fibrillation.

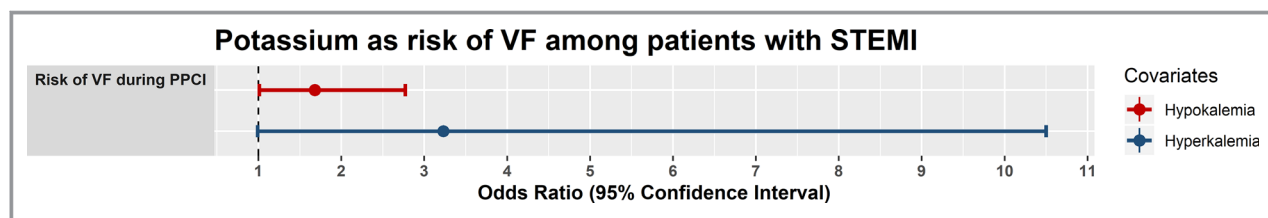


Figure 4. Potassium disturbances associated with ventricular fibrillation during PPCI among patients with STEMI who had potassium measurements immediately before primary percutaneous coronary intervention. PPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction, VF, ventricular fibrillation

patients with VF before PPCI in whom VF occurred after admission to the hospital. In this way, the time window between VF and potassium measurement would be short and the VF anticipated to be treated immediately. Compared with patients with normokalemia, patients with hypokalemia had increased risk of in-hospital VF before PPCI after adjusting for age, sex, and acute creatinine level. Patients with hyperkalemia had no increased risk of VF possibly because of lack of power ($n \leq 3$).

Patients with hyperkalemia had more cardiovascular comorbidities and higher use of various medications. Hence, hyperkalemia may be a marker of comorbidities and polypharmacy. Furthermore, acidosis following cardiac arrest or cardiogenic shock stimulates cellular efflux of potassium leading to hyperkalemia,²⁶ and patients with hyperkalemia were often Killip class $>I$. As epinephrine can lead to hypokalemia, a larger fraction of patients with hyperkalemia would be found in the normokalemia group. Hence, the risk estimates for VF among patients with hyperkalemia may be even greater than reported herein.

Prior myocardial infarction and diabetes mellitus was independently associated with reduced risk of VF before PPCI among patients with STEMI. This is a departure from our usual understanding.^{20,27} A possible explanation for this is that these patients may have more severe coronary artery disease which may influence the formation of collateral blood flow. However, data are conflicting whether diabetes mellitus enhance or impair the formation of collateral blood flow.^{28,29} Furthermore, recent studies suggest that the increase in risk of sudden cardiac arrest among patients with diabetes mellitus is not specific for sudden cardiac arrest, as diabetes mellitus also is associated with a similar increase in risk of death because of fatal (non-sudden cardiac arrest) coronary heart disease, and non-fatal myocardial infarction.^{30,31} Hence, patients with diabetes mellitus may not be at greater risk of VF in the setting of STEMI. On the other hand, as patients who do not survive to reach the hospital or who do not undergo PPCI are not included in this study, a proportion of patients with prior myocardial infarction and diabetes mellitus may not be included.

Strengths and Limitations

The strength of this study is the completeness of data via link between clinical data (the Eastern Danish Heart Registry) and Danish nationwide registries. Furthermore, this study was well-powered as the cohort was large, patients were enrolled consecutively, and the phenotype was refined by enrolling only STEMI patients with VF and distinguishing between VF before and during PPCI. Even though data were prospectively collected, a retrospective analysis was performed. Patients who died outside of hospitals were not included, and the results may not be generalizable to patients who do not survive to reach the hospital or who do not undergo angiography.

Given that the majority of patients had an out-of-hospital cardiac arrest (77%), quite a few variables were unaccounted for eg, medications given in the field by the emergency medical services personnel during resuscitation and time to return of spontaneous circulation which may have had an effect on the in-patient potassium levels.

Only absolute values for potassium levels were included and not fluctuations, which may be more accurate.³² Information on smoking status, Canadian Cardiovascular Society grading of angina pectoris, pre-procedural left ventricular ejection fraction, and magnesium levels in blood samples were missing for 12%, 9%, 80%, and 95% of patients, respectively, and thus could not be considered in the model. QT dispersion plays an important role for the pathophysiology of VF and/or polymorphic VT, however, information on QTc intervals from the ECG was not available and therefore adjustments could not be performed. Nevertheless, previously, in a subset of the cohort, no difference in QTc intervals was measured between STEMI patients with or without VF before PPCI.⁶ This is in line with the findings of others.^{33,34}

In the sensitivity analysis, patients with hyperkalemia did not have an increased risk of VF during PPCI possibly because of a lack of power. Moreover, VF during PPCI may be propagated by extensive manipulation (catheter maneuvers), coronary spasms, and reperfusion of the coronary artery and thus differ from the pathogenesis of VF before PPCI.

Clinical Implications

In the future, potassium measurements performed prehospital in the ambulance by arterial blood gas analysis would allow early detection and the opportunity for correction of potassium disturbances. This may reduce the risk of VF and subsequent death during acute ischemia. Further studies are needed to determine if correcting potassium disturbances among patients with STEMI will reduce the risk of VF.

Conclusions

Hypokalemia and hyperkalemia are associated with increased risk of VF in the early phase of STEMI (before PPCI). For hypokalemia, the association may be independent of the measurement of potassium before or after VF.

Sources of Funding

This work was supported by the European Union's Horizon 2020 Research and Innovation Program under grant agreement No 733381, the Novo Nordisk Foundation (grant number NNFOC140011573), Copenhagen, Denmark, The Heart Centre, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1: International Classification of Disease (ICD) codes (ICD-10 and ICD-8).

Comorbidity	ICD-10 and ICD-8 codes
Diabetes	ICD-10: E10-14 ICD-8: 250
Hypertension	ICD-10: I10-I15 ICD-8: 400-403
Hypercholesterolemia	ICD-10: E780 ICD-8: 27200, 27900
Peripheral vascular disease	ICD-10: I70, I74 ICD-8: 440, 444
Ischemic heart disease	ICD-10: I20-I25 ICD-8: 410-414
Prior myocardial infarction	ICD-10: I21, I22 ICD-8: 410
Congestive heart failure	ICD-10: I42, I50, I110, I130, I132 ICD-8: 425, 428, 4270, 4271
Atrial fibrillation	ICD-10: I48 ICD-8: 42793, 42794
Ischemic stroke	ICD-10: I63, I64 ICD-8: 432-434, 436
Chronic kidney disease	ICD-10: E102, E112, E132, E142, I120, N02-N08, N11, N12, N14, N18, N19, N26, N158-N160, N162-N164, N168, M300, M313, M319, M321B, Q612, Q613, Q615, Q619, T858, T859,

	<p>Z992</p> <p>ICD-8: 403, 404, 581-584, 25002, 40039, 59009, 59320, 75310, 75311, 75319</p>
Liver disease	<p>ICD-10: K70-77, K704, K711, K766, B150, B160, B190</p> <p>ICD-8: 456, 571, 572</p>

Table S2: Anatomical Therapeutic Chemical (ATC) classification codes.

Pharmacotherapy	ATC codes
Diuretics (combinational)	C03B, C07C, C08G, C09BA, C09DA
Loop diuretics	C03C, C03EB01, C03EB02
Thiazides	C02DA, C03A, C07B, C07D, C09XA52, C03EA01
Spironolactone	C03DA01
Potassium supplements	A12BA
Renin-angiotensin-system inhibitors	C09
Beta-blockers	C07, C09BX02
Antiadrenergic drugs	C02A, C02B, C02C
Calcium channel blockers	C08, C07FB, C09BB, C09DB
Anti-diabetics	A10
Statins	C10AA
Antiarrhythmic drugs class I and III	C01B

Table S3: A logistic regression model of risk of in-hospital ventricular fibrillation *before* primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction.

Variables	Contrast	Odds ratio	95% CI	p
Blood samples				
Hyperkalemia	Normokalemia	0.79	0.17-3.61	0.76
Hypokalemia	Normokalemia	2.23	1.60-3.11	<0.001
Creatinine	10 μ mol/L of increase	1.03	1.01-1.05	0.002
Age				
<50 years of age	\geq 80 years of age	1.28	0.62-2.65	0.51
50-80 years of age	\geq 80 years of age	1.70	0.93-3.12	0.08
Sex	Male vs. female	1.11	0.77-1.61	0.58

Table S4: Characteristics of patients with ST-segment elevation myocardial infarction (STEMI) with ventricular fibrillation *during* primary percutaneous coronary intervention (PPCI) who had potassium measurements immediately before PPCI (sensitivity analysis).

VARIABLES	Normokalemia 3.5-5.0 mmol/l (n=6229)	Hypokalemia <3.5 mmol/l (n=1593)	p Hypokalemia vs. normokalemia	Hyperkalemia >5.0 mmol/l (n=107)	p Hyperkalemia vs. normokalemia
Male sex, n (%)	4750 (76.3)	1016 (63.8)	<0.001	76 (71.0)	0.25
Median age, years [IQR]	63.1 [54.0, 72.3]	63.2 [53.7, 72.6]	0.86	70.3 [61.7, 78.9]	<0.001
Categorical age, n (%)					
<50 years	984 (15.8)	272 (17.1)	0.44	6 (5.6)	<0.001
50-80 years	4532 (72.8)	1146 (71.9)		77 (72.0)	
≥80 years	713 (11.4)	175 (11.0)		24 (22.4)	
Body mass index (BMI), kg/m²					

BMI ≥25, n (%)	3036 (62.4)	788 (64.3)	0.23	44 (61.1)	0.92
Smoking, n (%)					
Current	2866 (52.2)	667 (47.6)	<0.001	32 (42.7)	0.26
Past	1379 (25.1)	330 (23.6)		23 (30.7)	
Never	1249 (22.7)	403 (28.8)		20 (26.7)	
Canadian Cardiovascular Society (CCS) grading of angina pectoris, n (%)					
Class I-II	703 (12.2)	173 (11.7)	0.76	16 (18.6)	0.20
Class III-IV	555 (9.7)	138 (9.3)		8 (9.3)	
No angina	4487 (78.1)	1169 (79.0)		62 (72.1)	
<u>COMORBIDITIES</u> , n (%)					
Diabetes	743 (11.9)	139 (8.7)	<0.001	38 (35.5)	<0.001

Hypertension	1563 (25.1)	592 (37.2)	<0.001	54 (50.5)	<0.001
Hypercholesterolemia	1137 (18.3)	281 (17.6)	0.60	29 (27.1)	0.027
Peripheral vascular disease	257 (4.1)	35 (2.2)	<0.001	12 (11.2)	<0.001
Family history of ischemic heart disease	1663 (32.6)	431 (33.5)	0.55	18 (30.5)	0.84
Ischemic heart disease	1280 (20.5)	308 (19.3)	0.30	36 (33.6)	0.001
Prior myocardial infarction	782 (12.6)	161 (10.1)	0.008	27 (25.2)	<0.001
Congestive heart failure	292 (4.7)	56 (3.5)	0.05	13 (12.1)	<0.001
Atrial fibrillation	256 (4.1)	62 (3.9)	0.75	17 (15.9)	<0.001
Stroke	286 (4.6)	66 (4.1)	0.48	7 (6.5)	0.47
Chronic kidney disease	180 (2.9)	35 (2.2)	0.15	16 (15.0)	<0.001
Liver disease	82 (1.3)	26 (1.6)	0.40	≤3 (≤2.8)	0.94

<u>OUTCOMES, n (%)</u>					
Ventricular fibrillation during PPCI	84 (1.3)	38 (2.4)	0.004	5 (4.7)	0.013
<u>PHARMACOTHERAPY, n (%)</u>					
Diuretics (combinational)	244 (3.9)	167 (10.5)	<0.001	4 (3.7)	1.00
Loop diuretics	277 (4.4)	68 (4.3)	0.81	16 (15.0)	<0.001
Thiazides	331 (5.3)	230 (14.4)	<0.001	8 (7.5)	0.44
Spironolactone	61 (1.0)	8 (0.5)	0.10	7 (6.5)	<0.001
Potassium supplements	198 (3.2)	85 (5.3)	<0.001	11 (10.3)	<0.001
Renin-angiotensin-system blockers	1104 (17.7)	339 (21.3)	0.001	30 (28.0)	0.008
Beta-blockers	769 (12.3)	188 (11.8)	0.58	20 (18.7)	0.07
Anti-adrenergic drugs	53 (0.9)	16 (1.0)	0.66	0 (0.0)	0.67

Calcium channel blockers	684 (11.0)	303 (19.0)	<0.001	19 (17.8)	0.040
Antidiabetics	569 (9.1)	100 (6.3)	<0.001	30 (28.0)	<0.001
Statins	873 (14.0)	208 (13.1)	0.34	21 (19.6)	0.13
Antiarrhythmic drugs	7 (0.1)	0 (0.0)	0.38	≤3 (≤2.8)	<0.001
<u>BLOODSAMPLES</u>					
Acute creatinine, μmol/l [IQR]	77.0 [66.0, 92.0]	75.0 [63.0, 88.0]	<0.001	132.0 [97.0, 187]	<0.001
Troponin-T max, ng/L [IQR]	3550 [1380, 7470]	3740 [1490, 7650]	0.09	5615 [1985, 12600]	0.029
Time from symptom to Troponin-T max, hours [IQR]	13.9 [9.8, 18.7]	13.5 [9.5, 17.8]	0.038	15.5 [9.2, 21.0]	0.38

Missing: BMI 22%, Smoking 12%, Family history of ischemic heart disease 19%, CCS angina 8%, Acute creatinine 7%, Troponin-T max 21%, and Time from symptom to troponin-T max 21%.

Table S5: Angiographic and procedural characteristics of patients with ST-segment elevation myocardial infarction (STEMI) with ventricular fibrillation *during* primary percutaneous coronary intervention (PPCI) who had potassium measurements immediately before PPCI (sensitivity analysis).

VARIABLES	Normokalemia 3.5-5.0 mmol/l (n=6229)	Hypokalemia <3.5 mmol/l (n=1593)	p Hypokalemia vs. normokalemia	Hyperkalemia >5.0 mmol/l (n=107)	p Hyperkalemia vs. normokalemia
Time from symptom onset to PPCI, minutes [IQR]	191 [135-285]	151 [110-240]	<0.001	240 [154-385]	0.003
Preprocedural LVEF, n (%)					
≤35 %	243 (22.1)	72 (24.3)	0.45	19 (67.9)	<0.001
Infarct location, n (%)					
Anterior	2534 (43.4)	709 (47.6)	0.004	35 (39.3)	0.51
Non-anterior	3309 (56.6)	780 (52.4)		54 (60.7)	
Culprit lesion, n (%)					

LAD	2666 (43.0)	757 (47.6)	0.003	48 (44.9)	0.88
RCA	2644 (42.6)	633 (39.8)		43 (40.2)	
LCX	896 (14.4)	199 (12.5)		16 (15.0)	
Killip class, n (%)					
I	5502 (92.8)	1412 (92.2)	0.56	63 (64.9)	<0.001
II	251 (4.2)	77 (5.0)		8 (8.2)	
III	73 (1.2)	19 (1.2)		4 (4.1)	
IV	104 (1.8)	24 (1.6)		22 (22.7)	
Preprocedural TIMI flow, n (%)					

TIMI 0-I	3941 (63.7)	1077 (68.3)	<0.001	83 (78.3)	0.003
TIMI II-III	2248 (36.3)	500 (31.7)		23 (21.7)	
Postprocedural TIMI-flow, n (%)					
TIMI 0-I	147 (2.4)	42 (2.7)	0.58	5 (4.7)	0.22
TIMI II-III	6030 (97.6)	1536 (97.3)		101 (95.3)	

Missing: Time from symptom to procedure 15%, LVEF 82%, and Infarct location 6%, and Killip class 5%.

LVEF = Left ventricular ejection fraction, LAD = Left anterior descending artery, RCA = Right coronary artery, LCX = Left circumflex artery, TIMI = Thrombolysis in myocardial infarction.

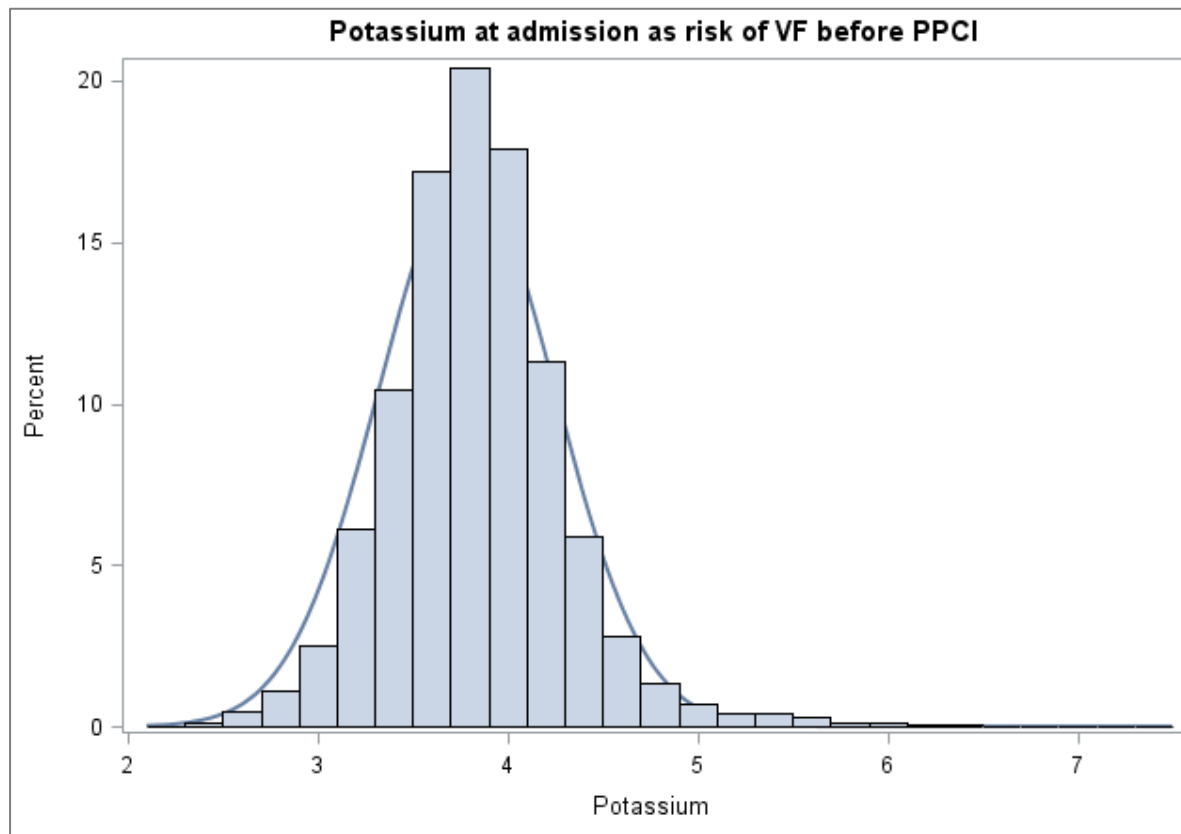
Table S6: A logistic regression model of risk of ventricular fibrillation *during* primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction.

Variables	Contrast	Odds ratio	95% CI	p
Blood samples				
Hyperkalemia	Normokalemia	3.23	0.99-10.50	0.05
Hypokalemia	Normokalemia	1.68	1.01-2.77	0.045
Creatinine	10 μ mol/L of increase	1.00	1.00-1.01	0.13
Troponin-T max	1000 ng/L of increase	1.03	1.00-1.05	0.024
Age				
<50 years of age	\geq 80 years of age	0.74	0.31-1.80	0.51
50-80 years of age	\geq 80 years of age	0.82	0.42-1.61	0.57
Sex	Male vs. female	0.95	0.57-1.60	0.86
Hypertension	Yes vs. no	0.96	0.51-1.83	0.91
Prior myocardial infarction	Yes vs. no	0.69	0.28-1.69	0.42
Congestive heart failure	Yes vs. no	1.05	0.29-3.88	0.94
Atrial fibrillation	Yes vs. no	0.49	0.11-2.21	0.35

Diabetes	Yes vs. no	0.47	0. 81-1.22	0.12
Peripheral vascular disease	Yes vs. no	<0.01	<0.01- >999.99	0.97
Killip class >I at admission	Killip class I	2.67	1.45-4.91	0.002
Culprit	LAD vs. non-LAD	0.55	0.34-0.90	0.017
Preprocedural TIMI-flow	TIMI 0-I vs. II-III	2.98	1.55-5.72	0.001
Loop diuretics	Yes vs. no	1.27	0.41-3.94	0.68
Combinational diuretics	Yes vs. no	0.75	0.24-2.32	0.61
Thiazides	Yes vs. no	0.97	0.39-2.42	0.94
Spironolactone	Yes vs. no	<0.01	<0.01- >999.99	0.99

TIMI= Thrombolysis in myocardial infarction, LAD = Left anterior descending artery.

Figure S1: Distribution of potassium measurements (mmol/L) immediately before primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction.



Median	Mean	Lower Quartile	Upper Quartile	Minimum	Maximum	Std. Dev.
3.80	3.79	3.50	4.00	2.10	7.40	0.47